Background

Following the review of stability for cytotoxic drugs for the NHS tender, these monographs are designed to capture the information in a format that is useful for NHS aseptic units, particularly those working under Section 10 exemption with restricted shelf lives for products. There is also, where applicable, a view on the extended data beyond the maximum seven days that can be assigned under Section 10 exemption. This may be of use to licensed NHS aseptic units and also to procurement staff in terms of assessing the shelf lives assigned by commercial aseptic compounding units.

The studies provided have been reviewed against the standards of the NHS standards for stability testing of small molecule drug aseptic products[1].

Drug: Vinorelbine

CMU requirements for shelf life (taken from Wave 12 tender)

Seven days shelf-life at up to 1.2mg/ml in sodium chloride 0.9% infusion bag

British Pharmacopoeia specification for product. General BP requirements (e.g. Parenteral Preparations Monograph) also apply.

BP 2020 monograph for Vinorelbine Tartrate API but not for the injection.

BP limits for related substances in the API

impurity A: maximum 0.3%
impurities C, I, K: for each impurity, maximum 0.2%
unspecified impurities: for each impurity, maximum 0.10%
total: maximum 0.5%

Assessment:

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Accord Healthcare PL 0142/1231	The physicochemical and microbiological stability of the drug product after dilution in the recommended solutions for infusion (sodium chloride 0.9% or glucose 5%) has been demonstrated for 24 hours at 2-8°C and 25°C.	Concentrate for solution for infusion Water for injections	Study 0.5 - 0.76 - 1.21 - 3mg/ml in bags, 0.1 - 0.2mg/ml in syringe. Lack of replicates but a lot of different samples and all showing consistency. Study for 28 days in bags, 7 days in syringes in a refrigerator, room temperature (20 – 25°C) data for 4 days, saline and dextrose. Lack of data points, only 2 or 3 post T=0, no sub-visible particles, no degradation product analysis[2]	Concentrations between 0.5 – 3mg/ml can be assigned a seven-day shelf life, stored at 2 – 8°C protected from light. Can go down to 0.1mg/ml in syringes.	Some data for extended shelf life of up to 28 days see below.
Medac PL 11587/0036	Chemical and physical in use stability has been demonstrated for 24 hours at 2-8 °C and at 25 °C.	Concentrate for solution for infusion Water for injections	Study 0.5 - 3.0mg/ml gives a shelf life of 28 days in the refrigerator or room temperature protected from light. (Product shows significantly increased degradation products without light protection). No replicates although multiple variations and consistent data across the study, no sub-visible particles, good degradation product analysis[3].	Concentrations between 0.5 – 3mg/ml can be assigned a seven-day shelf life, stored at 2 – 8°C protected from light.	Some data for extended shelf life of up to 28 days see below.

Manufacturer	SmPC shelf life	Excipients / formulation details	Assessment of Extended studies submitted	Shelf-life recommendation (section 10 units)	Comments on further shelf life extension
Pierre Fabre Ltd PL 00603/0028	After diluting saline or glucose, chemical and physical in-use stability has been demonstrated for 8 days at room temperature (20°C ± 5°C) or in the refrigerator (2°C – 8°C) protected from light, in neutral glass bottle, PVC and vinyl acetate bags	Concentrate for solution for infusion Water for injections Filled under Nitrogen	N/A	SmPC shelf life can be extrapolated to polyolefin bags. Seven-day shelf life can be assigned, stored at 2 – 8°C protected from light	See below

Conclusions (based on the data supplied)

The three products are all just simple solutions of Vinorelbine in water for injection. The SmPCs for Accord and medac only assign 24 hours but both companies supplied additional data for between seven and twenty-eight days, neither paper included sub-visible particle counts but the medac study did include analysis of degradation products. All three products can safely be assigned a shelf life of seven days for the diluted product stored at 2 – 8°C protected from light in the concentration range 0.5 – 3.0mg/ml, potentially lower concentrations in syringes if necessary. There is data to support an extended shelf life of up to 28 days based on the Medac product which included the degradation product profile and showed no loss of active over the study duration. Impurity A 3,6-Epoxyvinorelbine was within the API specification throughout as were other named impurities, one unnamed impurity did slightly exceed the BP limit of 0.1% but remember these are limits for the API, the total impurities level was within BP limits. If using this extended data then it is recommended that sub-visible particles be measured at the end of the shelf-life to ensure compliance with specifications.

Published and other studies

Compatibility of plastics with cytotoxic drug solutions - comparison of polyethylene with other container materials: Int J Pharm ; 185: 113-121. 1999, Beitz C, Bertsch T, Hannak D, Schrammel W, Einberger C, Wehling M[4]

The study looked at a variety of cytotoxic drugs including Virorelbine at a fixed concentration of 0.385mg/ml in Sodium chloride 0.9% infusion stored at room temperature in a variety of container types and showed no loss of active over the seven-day period. Other factors such as degradation products and sub-visible particle counts were not included in the study.

Five-day stability of vinorelbine in 5% dextrose injection and in 0.9% sodium chloride injection at room temperature: Int J Pharm Compound ; 3: 67-68. 1999, Lieu CL, Chin A, Gill MA.[5]

The study covered the concentration range of 0.5 – 2.0mg/ml in sodium chloride 0.9% and dextrose 5% in PVC minibags stored at room temperature in constant fluorescent light for five days and was examined physically and by HPLC. There was no reporting of degradation product profiles and from the above (Medac) study we know that light exposure does cause an increase in degradation products. The study also allowed 6% loss of active over the period.

These published studies do not add anything to the data submitted and discussed above.

Assessment carried out and report written by

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References

1. A Standard Protocol for Deriving and Assessment of Stability Part 1 – Aseptic Preparations (Small molecules) Edition 5, September 2019 (NHS PQA Committee)
2. Physical and Chemical in-use stability of Vinorelbine 10mg/ml Concentrate for solution for infusion, 29/07/15, Accord
3. Navirel® 10 mg/ml concentrate for solution for infusion - Vinorelbine 10 mg/ml Concentrate for solution for infusion - Guidelines for the Safe Handling and Drug Stability Information, October 2015, medac
4. Compatibility of plastics with cytotoxic drug solutions - comparison of polyethylene with other container materials: Int J Pharm ; 185: 113-121. 1999, Beitz C, Bertsch T, Hannak D, Schrammel W, Einberger C, Wehling M
5. Five-day stability of vinorelbine in 5% dextrose injection and in 0.9% sodium chloride injection at room temperature: Int J Pharm Compound ; 3: 67-68. 1999, Lieu CL, Chin A, Gill MA.